REMARKS

Upon entry of the foregoing amendment, Claims 1, 3-8, 12, 13, 15 and 20-22 will remain pending in the application. Claims 10, 14, and 17-19 have been canceled; Claims 1, 3, 15, 20-22 have been amended. The amendments are supported by the specification at least on page 7, lines 6-9. These changes do not introduce new matter, and their entry is respectfully requested.

In the Advisory Action dated March 11, 2009 and the Office Action dated December 31, 2008, the Examiner sets forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Abstract

The abstract is objected to because it is insufficiently detailed with respect to the claimed method of preparing the conjugate. The abstract has been amended to provide more detail to the method for preparing the conjugate.

Objections Under 37 C.F.R. 1.121 (c) (2)

The amendments in Claims 3 and 19 stand objected because they are not in compliance with 37 C.F.R. 1.121 (c) (2). Claim 3 has been amended to address the Examiner's concerns. Claim 19 has been canceled.

The grounds for objection have been obviated and withdrawal of Objections Under 37 C.F.R. 1.121 (c) (2) is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 21 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that there is no antecedent basis in the claim for the phrase "said organ transplantation" at Claim 21, line 1. Claim 21 has been amended to depend from Claim 7, as suggested by the Examiner.

Applicant respectfully submits that the amendment obviates the grounds for the rejection. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 3-8, 10, 12-14 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, for non-enablement. Specifically, the Examiner alleges that the specification, while being enabling for the prevention of transplantation-associated immune responses, does not reasonably provide enablement for the treatment of transplantation-associated immune responses. In order to expedite prosecution, independent Claim 1 has been amended to recite a method for preventing a transplantation-associated immune response.

Applicant respectfully submits that the amendment obviates the grounds for the rejection. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 1, 3-8, 10, and 12-14 stand rejected under 35 U.S.C. § 102(b) over the Wolff et al. abstract (Blood, Vol. 102, No. 11, page 404b) (hereinafter "Wolff") for the reasons set forth on pages 4-5 of the Office Action. Applicant respectfully traverses the rejections.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In this case, independent Claim 1, as amended, recite a method for preventing a transplantation-associated immune response in a subject, comprising administering to said subject an effective amount of a conjugate comprising methotrexate and albumin at a **methotrexate:albumin molar ratio of 1:1000 to 2:1**.

In contrast, Wolff generally describes the use of a methotrexate-albumin conjugate for the modulation of a transplantation-associated immune reaction. Wolff, however, does not provide any information as to the molar ratio of the carrier albumin and the active agent methotrexate. The inventor of the present application found out that the molar ratio of a conjugate is essential for the efficacy of the conjugate (Applicant would like to submit the expert Declaration under 37 C.F.R. 1.132 showing that the molar ratio of a conjugate is essential for the efficacy of the conjugate).

It has been assumed in the art that loading of albumin with a high dosage of therapeutically active agents is necessary in order to achieve a therapeutic response. The problem with high-loaded albumin, however, is that in such conjugates, albumin is not present in its native active form but in a

denatured form, which results in albumin being recognized as foreign by the body and rapidly eliminated (Stehle G, Sinn H, Wunder A, Schrenk HH, Schiitt S, Heene DL, Maier-Borst W. The loading rate determines tumor targeting of methotrexate-albumin conjugates in rats. Anticancer Drugs 8:677-685, 1997). In humans, an immunological reaction which might be life-threatening is to be expected upon repeated administration of such high-loaded albumin. For a clinical application of the conjugates, it is, therefore, decisive that albumin is present in the native form since only its native form has the desired properties to accumulate especially at sites of infectious processes but not in healthy tissues. Only if albumin is present in a native form, it can act as a transporter and transport the active substance with which it is loaded to the desired effective site (See Expert Declaration).

Accordingly, Claim 1 is patentable over Wolff because Wolff does not mention anything about the methotrexate:albumin molar ratio in the methotrexate-albumin conjugate. Claims 3-8, 12 and 13 are patentable because they depend from Claim 1. Claims 10 and 14 have been canceled.

In view of the foregoing, Applicant respectfully submits that the grounds for the rejections have been obviated. Withdrawal of the rejections under 35 U.S.C. §102 (b), is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 15, 17, 18 and 20 stand rejected under 35 U.S.C. § 103(a) over the Sutton et al. (US 5,993,805) (hereinafter "Sutton") in view of the European Patent Application (EP0282057) (hereinafter "EP0282057") for the reasons set forth on pages 5-6 of the Office Action. Claims 19 and 22 stand rejected under 35 U.S.C. § 103(a) over the Sutton

et al. (US 5,993,805) (hereinafter "Sutton") in view of the European Patent Application (EP0282057) (hereinafter " Application '057") or Low et al. (US 5,688,488) (hereinafter "Low") for the reasons set forth on page 6 of the Office Action. Applicant respectfully traverses the rejections.

To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka,* 490 F. 2d981, 180 USPQ 580 (CCPA, 1974).

In this case, independent Claim 15, as amended, is directed to a method for preparing a conjugate comprising methotrexate and albumin, said method comprising: activating methotrexate with 1-ethyl-3-(3-dimethylaminopropyl) carbonyldiimide in an organic solvent, and reacting activated methotrexate with albumin at **a methotrexate:albumin molar ratio of 10:1 to 1:10**.

In contrast, Sutton generally describes the production of a methotrexate/albumin conjugate. However, Sutton does to teach or suggest reacting activated methotrexate with albumin at a methotrexate:albumin molar ratio of 10:1 to 1:10, as recited in Claim 15.

EP0282057 and Low do not cure the deficiency of Sutton. EP0282057 generally describes a method for coupling methotrexate to an antibody. Nonetheless, EP0282057 neither mentions coupling methotrexate to albumin nor a methotrexate:albumin molar ratio of 10:1 to 1:10.

Low generally describes coupling activated folic acid to bovine ribonuclease. Similarly, Low fails to teach or suggest coupling methotrexate to albumin, let alone reacting activated methotrexate with albumin at a methotrxate:albumin molar ratio of 10:1 to 1:10, as recited in Claim 15.

None of the above references cited by the Examiner mentioned the methotrexate:albumin molar ratio in the final conjugate. Further, as discussed above, it has been assumed in the art that loading of albumin with a high dosage of therapeutically active agents is necessary in order to achieve a therapeutic response. Nonetheless, with high-loaded albumin in conjugates, albumin is not present in its native active form but in a denatured form, which results in albumin being recognized as foreign by the body and rapidly eliminated (Stehle G, Sinn H, Wunder A, Schrenk HH, Schiitt S, Heene DL, Maier-Borst W. The loading rate determines tumor targeting of methotrexate-albumin conjugates in rats. Anticancer Drugs 8:677-685, 1997). Also, discussed above, only if albumin is present in a native form, it can act as a transporter and transport the active substance with which it is loaded to the desired effective site.

The inventor of the present application, Sinn, found that it is important to load albumin with an active ingredient, especially methotrexate, only to a particular degree. Specifically, the methotrexate :albumin molar ratio of the methotrexate-albumin conjugates is preferably 1:1000 to 2:1, more preferably 1:100 to 1.1:1, and most preferably 0.9:1 to 1.1:1. In such loading, albumin still shows native behavior, which is essential for the efficacy of the methotrexate-albumin conjugates in modulating a transplantation-associated immune response. The application further describes that a conjugate with a preferred methotrexate:albumin ratio can be prepared by reacting activated methotrexate with albumin at a molar ratio of 10:1 to 1:10.

Neither Sutton, EP0282057 nor Low mentions the methotrexate:albumin molar ratio in the final conjugate. Consequently, the unexpectedly superior effect of the claimed conjugate render it particularly well suited for the prevention of a transplantation associated immune response. One skilled in the art would not be able to produce the Claimed invention based on Sutton,

EP0282057 and Low without undue experimentation. Thus, it is not obvious to one skilled in the art to derive the present invention from the prior art of record.

Accordingly, Claim 15 is patentable over Sutton, EP0282057 and Low. Claims 17, 18 and 20 are patentable over Sutton, EP0282057 and Low because they depend from Claim 15 and recite additional patentable subject matter.

In view of the foregoing, Sutton, EP0282057 and Low do not support a *prima facie* case of obviousness. Applicant respectfully submits that the grounds for the rejections have been obviated and withdrawal of the rejections under 35 U.S.C. §103 (a), is respectfully requested.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Applicant's counsel, Ping Wang, M.D. (Reg. No. 48,328), at 202.842.0217.

Respectfully submitted,

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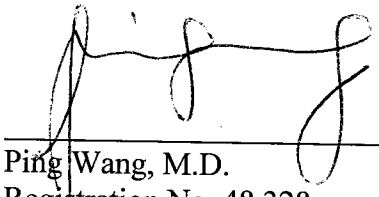

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